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ANTIDEPRESSANT AGENTS WITH A RAPID ONSET OF ACTION

Abstract:

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(A1) Translate this text A selective serotonin reuptake inhibitor such as sertraline is used in combination with lithium for simultaneous or separate, including concurrent, administration in a method of achieving rapid onset of antidepressant action in a patient. Onset of antidepressant action is observed with such preparations approximately one week earlier than that achievable through the administration of the selective serotonin reuptake inhibitor alone. Such rapid onset of action is extremely significant in the case of patients who are severely depressed.

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(57) Abstract

A selective serotonin reuptake inhibitor such as sertraline is used in combination with lithium for simultaneous or separate, including concurrent, administration in a method of achieving rapid onset of antidepressant action in a patient. Onset of antidepressant action is observed with such preparations approximately one week earlier than that achievable through the administration of the selective serotonin reuptake inhibitor alone. Such rapid onset of action is extremely significant in the case of patients who are severely depressed.

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Description

Antidepressant agents with a rapid onset of action

Technical Field

This invention relates to agents effective in the treatment of depression and, in particular, to combinations of antidepressant agents effective in achieving a rapid onset of antidepressant action.

Background Art

Medications effective in the treatment of depressive illness first emerged in the 1950s with the development of monoamine oxidase inhibitors and tricyclic antidepressants. Since then the tricyclic antidepressants such as amitriptyline and imipramine have been the mainline treatment for depressive illness. The major limitations of these drugs include the fact that they have a high incidence of side effects, are dangerous when taken in overdose and on average take three to six weeks to produce a therapeutic effect. This delayed onset of action can be extremely significant if a patient is severely depressed.

Recently a group of drugs has emerged with antidepressant effect, whose mode of action is to selectively block the reuptake of serotonin. These drugs include sertraline, fluoxetine, fluovoxamine, paroxetine and citalopram. In contrast to the tricyclic antidepressants they have a low incidence of side effects and are safe when taken in overdose, but they also take at least two to three weeks to produce a therapeutic response.

It has long been recognised that the addition of lithium to an antidepressant in a patient who is treatment non-responsive may produce a dramatic improvement in their mental state (De Montigny, C., *et al.* (1981); Br. J. Psychiatry *138*: 252-256; Dinan, T.G. and Barry, S. (1989); Acta Psychiatr. Scand. *80*: 97-100). It has become standard clinical practice to add lithium to a tricyclic antidepressant or

a selective serotonin reuptake inhibitor when the patient is failing to respond to treatment for depression.

In a previous study we found that approximately two out of every three treatment non-responsive patients responded when lithium was added to the antidepressant agent (Dinan, T.G. and Barry, S. (1989) *supra*). In such circumstances lithium is added in doses which give a blood level around 0.7 to 0.8 mmol/l (0.7 to 0.8 mEq/l) (De Montigny, C., *et al.* (1981) *supra*).

Despite the advances in the pharmacology of depression which have taken place recently, no drug to date can produce a clinically significant improvement in depressive symptomatology faster than amitriptyline i.e. at least two to three weeks.

Accordingly, there is a need for medicaments which have an onset of antidepressant action faster than that of antidepressant agents currently available, specifically faster than that of amitriptyline which as indicated above has an onset of action of at least two to three weeks.

Also as indicated above, a delayed onset of action can be extremely significant if a patient is severely depressed with the ensuing consequences outlined above. There is also a need to produce a broader spectrum antidepressant. At present effective antidepressants help approximately 60-70% of depressed patients.

Disclosure of the Invention

We have found that the treatment of depression with a combination of a selective serotonin reuptake inhibitor and a low dose of lithium results in a more rapid onset of antidepressant action than heretofore achievable and a response in a greater number of patients than expected.

The invention provides a product containing a selective serotonin reuptake inhibitor and lithium as a combined preparation for

simultaneous or separate use in a method of achieving rapid onset of antidepressant action in a patient.

More especially, the onset of antidepressant action is achievable with products in accordance with the invention approximately one week earlier than that achievable through use of the selective serotonin reuptake inhibitor alone.

Suitable selective serotonin reuptake inhibitors are selected from sertraline, fluoxetine, fluovoxamine, paroxetine and citalopram.

For ease of patient compliance, the selective serotonin reuptake inhibitor and the lithium are combined in a single unit dosage form for simultaneous administration. However, two separate preparations can also be administered as in the case of separate, including concurrent, administration.

The product in accordance with the invention can be administered by any route normally used in the administration of the respective components thereof. In the case of oral administration, the respective components either separately or in combination can be administered in the form of capsules, tablets or other suitable oral dosage form.

We have recently found that far lower doses of lithium than previously described are effective in treating resistant depression. We studied a sample of patients who were resistant to treatment with sertraline. Half the sample were treated with lithium 400 mg *nocte* and the remainder with 800 mg *nocte*. The outcome in both groups was essentially the same and those patients given 400 mg of lithium *nocte* had blood levels around 0.2 mmol/l (0.2 mEq/l).

Thus in the product according to the invention, the lithium is used in an amount effective to achieve blood levels of lithium of the order of 0.2 mmol/l (0.2 mEq/l) or greater. The benefit of this low dose is to minimize toxicity and the need for plasma level monitoring.

The results from the aforementioned recent study suggest strongly that lithium augmentation of a selective serotonin reuptake inhibitor occurs at a dose considerably lower than previously considered to be therapeutic.

Modes for Carrying Out the Invention

When the selective serotonin reuptake inhibitor (SSRI) is sertraline, the product will suitably contain 25 mg of sertraline and 400 mg lithium in the form of a pharmaceutically acceptable salt thereof such as lithium carbonate or other pharmaceutically acceptable lithium salt. In the case of other SSRIs the following doses should be used, for example, fluoxetine 5 mg and paroxetine 10 mg.

Our recent study led us to hypothesise that the treatment of depression with a combination of a selective serotonin reuptake inhibitor such as sertraline and a low dose of lithium would result in a more rapid onset of antidepressant action. A preliminary open study described further below and involving eight patients treated concomitantly with sertraline (25 mg daily) and lithium (400 mg *nocte*) was found to support this hypothesis. Thus, the use of lithium in conjunction with the antidepressant sertraline produced a therapeutic effect approximately one week prior to what one would normally have expected.

The invention further provides use of a selective serotonin reuptake inhibitor and lithium in the manufacture of a medicament for use in the treatment of depression, wherein the medicament is administered at the commencement of treatment to bring about a rapid onset of antidepressant action.

Preliminary open study

Eight patients, six female and two male, aged 26 to 56 years with a DSM-III (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders) (3rd Ed. Washington D.C.: APA)

diagnosis of major depression were included. They had Hamilton depression scores (Hamilton, M. (1960); A rating scale for depression J. Neurol. Neurosurg. Psychiatry *23*, 56-62) ranging from 21-27. They were each treated with sertraline (25 mg daily) and lithium (400 mg *nocte*) for a total of 6 weeks. Clinical ratings were made once weekly. Seven of the eight patients responded to the treatment. (Response was defined as a Hamilton score below 8 or at least a 50% decrease in baseline scores). Four patients responded by the end of week 1, two at the end of week 2 and one at the end of week 3.

Further open study

It is generally accepted that there are 5HT abnormalities in depressive illness. These abnormalities can be demonstrated in several ways. A frequently used approach is to make use of the fact that 5HT stimulates prolactin release from the anterior-pituitary gland. Several drugs, including d-fenfluramine have been used to stimulate prolactin release through this mechanism. The extent of prolactin release is an index of the responsivity of the serotonergic system. Depressed patients show blunted responses and normalisation of the response parallels clinical improvement.

Five patients with major depression underwent d-fenfluramine/ prolactin stimulation tests. The test was carried out in each case at 9 am, at which time the patient was cannulated and had baseline blood samples for prolactin estimation drawn. They were then given d-fenfluramine 30 mg orally and further blood samples for prolactin estimation were drawn over a 5 hour period. Patients were then treated with sertraline (50 mg) and lithium (400 mg nocte) for one week. They then underwent a further d-fenfluramine/prolactin stimulation test. Overall, there was a significant increase in responsivity on the second test. This contrasts with a previous study where patients were treated with selective serotonin reuptake inhibitors alone. Under such circumstances alterations in serotonergic responsivity take 2-3 weeks to emerge. This finding provides further

evidence that the combined use of sertraline and lithium hastens the biological process of recovery in depression.

Claims:

1. A product containing a selective serotonin reuptake inhibitor and lithium as a combined preparation for simultaneous or separate use in a method of achieving rapid onset of antidepressant action in a patient.

2. A product according to Claim 1, which is effective to achieve onset of antidepressant action approximately one week earlier than that achievable through use of the selective serotonin reuptake inhibitor alone.

3. A product according to Claim 1 or 2, wherein the selective serotonin reuptake inhibitor is selected from sertraline, fluoxetine, fluovoxamine, paroxetine and citalopram.

4. A product according to Claim 3, wherein the selective serotonin reuptake inhibitor is sertraline.

5. A product according to any one of Claims 1-4, wherein the selective serotonin reuptake inhibitor and the lithium are combined in a single unit dosage form.

6. A product according to Claim 5, wherein the lithium is used in an amount effective to achieve blood levels of lithium of the order of 0.2 mmol/l (0.2 mEq/l) or greater.

7. A product according to any one of Claims 4-6, which contains 25 mg of sertraline and 400 mg of lithium in the form of a pharmaceutically acceptable salt thereof.

8. Use of a selective serotonin reuptake inhibitor and lithium in the manufacture of a medicament for use in the treatment of

depression, wherein the medicament is administered at the commencement of treatment to bring about a rapid onset of antidepressant action.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ACTA PSYCHIATR. SCAND. vol. 88 , August 1993 pages 300 - 301 T.G. DINAN 'lithium augmentation in sertraline-resistant depression: a preliminary dose-response study' * see the whole document * ---	1-8
X	ACTA PSYCHIATR. SCAND. vol. 83 , 1991 pages 188 - 192 A. ONTIVEROS ET AL. 'Refractory depression: the addition of lithium to fluoxetine or desipramine' * see the whole document * --- -/--	1-3,6

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AM. J. PSYCHIATR. vol. 145 , 1988 H.G. POPE ET AL. 'Possible synergism between fluoxetine and lithium in refractory depression' ---	1-3,6
X	J. AFFECT. DISORDERS vol. 15 , 1988 pages 55 - 60 P.L. DELGADO ET AL. 'Efficacy of fluvoxamine in treatment- refractory depression' * see the whole document * ---	1-3
A	MüNCH. MED. WSCHR. vol. 134 , 1992 pages 808 - 811 A. MACKERT 'Psychopharmakologische Kombinationen bei depressiven Erkrangungen' * see table 1 * ---	1
X	L'ENCEPHALE vol. 17 , 1991 pages 213 - 219 A. SOUCHE ET AL. 'traitement de la dépression résistante par l'association citalopram-lithium' -----	1-3